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REVIEW

Tail regeneration and other phenomena of wound healing and tissue restoration in lizards

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ABSTRACT

Wound healing is a fundamental evolutionary adaptation with two possible outcomes: scar formation or reparative regeneration. Scars participate in re-forming the barrier with the external environment and restoring homeostasis to injured tissues, but are well understood to represent dysfunctional replacements. In contrast, reparative regeneration is a tissue-specific program that near-perfectly replicates that which was lost or damaged. Although regeneration is best known from salamanders (including newts and axolotls) and zebrafish, it is unexpectedly widespread among vertebrates. For example, mice and humans can replace their digit tips, while many lizards can spontaneously regenerate almost their entire tail. Whereas the phenomenon of lizard tail regeneration has long been recognized, many details of this process remain poorly understood. All of this is beginning to change. This Review provides a comparative perspective on mechanisms of wound healing and regeneration, with a focus on lizards as an emerging model. Not only are lizards able to regrow cartilage and the spinal cord following tail loss, some species can also regenerate tissues after full-thickness skin wounds to the body, transections of the optic nerve and even lesions to parts of the brain. Current investigations are advancing our understanding of the biological requirements for successful tissue and organ repair, with obvious implications for biomedical sciences and regenerative medicine.

KEY WORDS: Cartilage, Reptile, Neurogenesis, Spinal cord, Skin, Blastema

Introduction

Wound healing is an essential biological process involving the synchronized orchestration of numerous cellular and molecular events (Gurtner et al., 2008; Seifert et al., 2012b; Peacock et al., 2015). While many of the key mechanisms involved in wound healing [including re-epithelialization (see Glossary), cell proliferation, angiogenesis, and extracellular matrix (ECM) deposition and remodeling] are widely conserved, the fidelity of repair often varies (Seifert et al., 2012a,b; Peacock et al., 2015). For example, in humans and most other mammals, non-lethal injuries typically result in the replacement of damaged tissues with a fibrous substitute known as a scar (see Glossary). Although scars participate in re-establishing homeostasis and barrier functions, they lack the organization, tensile strength and specialized functions of the original tissues (Ferguson and O'Kane, 2004; Corr et al., 2009; Yates et al., 2011). In contrast, other vertebrates – including various species of bony fish (teleosts), salamanders and lizards – are capable of wound healing without scar formation (e.g. Lévesque et al., 2010; Seifert et al., 2012b; Peacock et al., 2015; Unguez, 2015; Monaghan et al., 2014; Chen et al., 2016) (Table 1). Instead of replacing damaged tissue with a fibrous infill, these species undergo a tissue-specific program to restore tissue architecture and function. Although vertebrates lack the capacity for whole-body regeneration (see Glossary; unlike some species of invertebrates; Bely and Nyberg, 2010), a broad range of organs can be partially replaced, including portions of the skin (epidermis and dermis), heart (ventricle), forebrain (telencephalon), spinal cord and even multi-tissue appendages, such as limbs and the tail (Table 1).

Although it may be tempting to summarize scar-forming versus scar-free wound healing responses simply along phylogenetic lines (i.e. mammals scar, salamanders and lizards do not), the reality is far more complex. Fetal mammals can heal cutaneous wounds scar-free prior to the early- to mid-gestation period (Whitby and Ferguson, 1991; Lorenz et al., 1993; Ferguson and O'Kane, 2004), while postnatal mice, rats, rhesus monkeys and human children can also spontaneously regenerate amputated digit tips (the distal phalanx: Fernando et al., 2011; see reviews by Shieh and Cheng, 2015; Simkin et al., 2015). In addition, several species of African spiny mice (*Acomys* spp.) are able to perfectly heal holes created in their ears (Gawriluk et al., 2016; Matias et al., 2016), and even lose and then regenerate large portions of skin (~60% of the total dorsal body surface area; Seifert et al., 2012a). Clearly, the mechanisms involved in scar-free wound healing and regeneration are taxonomically widespread, which leads to the riddle: why are some tissues, structures and species able to regenerate, whereas others cannot? Although the answer remains elusive, significant progress has been made in better understanding the biology of self-repair and regeneration, drawing on an ever-increasing number of non-traditional models, including various species of lizards. In this Review, we focus on introducing lizards as a powerful and yet often overlooked vertebrate model for the study of wound repair and tissue replacement. We begin by considering the benefits of the lizard model, followed by a discussion of select examples of the wound healing and regenerative responses of lizards to injury. Our goals are to highlight how lizards can inform, enhance and expand our understanding of the biology of regeneration, and to demonstrate how lessons from our scaly relatives hold unexpected opportunities for probing endogenous mechanisms of tissue restoration.

Why lizards?

As a model system to study healing and regeneration, lizards offer several distinct advantages. Firstly, although best known for replacing the tail (Arnold, 1984; Bellairs and Bryant, 1985; McLean and Vickaryous, 2011; Lozito and Tuan, 2017; see below), some lizard species can also regenerate skin (Wu et al., 2014; Peacock et al., 2015), the optic nerve (Beazley et al., 1997) and even cell populations within the forebrain (Font et al., 1991,

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Journal of Experimental Biology (2017) 220, 2858-2869 doi:10.1242/jeb.126862

Table 1. A taxonomic survey of regeneration across vertebrates

Taxon	Species	Life stage	Tissue/organ	Mechanism(s)	Source
Basal vertebrates	Sea lamprey (*Petromyzon marinus*)	Larva	Spinal cord	Axonogenesis, neurogenesis	Selzer, 1978; Zhang et al., 2014; Rasmussen and Sagasti, 2017
Chondrichthyes (sharks, rays)	Nurse shark (*Ginglymostoma cirratum*), leopard shark (*Triakis semifasciata*)	Adult	Skin	Re-epithelialization, skeletogenesis [to replace scales (odontodes)]	Reif, 1978
Cladistia (basal ray-finned fish)	Bichir (*Polypterus senegalus*, *P. ornatipinnis*)	Juvenile	Multi-tissue pectoral fins	Blastema-mediated cell proliferation, chondrogenesis	Cuervo et al., 2012; Nikiforova and Golichenkov, 2012
Teleostei (true bone ray-finned fish)	Brown ghost knifefish (*Apteronotus leptorhynchus*)	Adult	Brain (cerebellum)	Neurogenesis	Zupanc and Zupanc, 2006; Sirbulescu and Zupanc, 2010; Allen and Smith, 2012
	Brown ghost knifefish (*Apteronotus leptorhynchus*)	Adult	Multi-tissue tail, including spinal cord	Blastema-mediated cell proliferation, axonogenesis, angiogenesis, chondrogenesis, myogenesis	Zupanc and Zupanc, 2006; Sirbulescu and Zupanc, 2010; Allen and Smith, 2012; Vitalo et al., 2016
	Multiple species, including goldfish (*Carassius auratus*), zebrafish (*Danio rerio*)	Adult and larva	Body spinal cord	Axonogenesis, ependymal tube outgrowth, neurogenesis	Sharma et al., 1993; Becker et al., 1997; see also Sirbulescu and Zupanc, 2011
	Zebrafish (*Danio rerio*)	Adult and larva	Skin	Re-epithelization, cell proliferation, angiogenesis, fibrogenesis	Richardson et al., 2013; Richardson et al., 2016
	Zebrafish (*Danio rerio*)	Adult and larva	Heart (ventricle)	De-differentiation, organ-wide and blastema-mediated cell proliferation, myogenesis, angiogenesis	Poss et al., 2002; Jopling et al., 2010; Han et al., 2014; Sallin et al., 2015
Dipnoi (lungfish)	African lungfish (*Protopterus annectens*, *P. aethiopictus*); South American lungfish (*Lepidosiren paradoxa*)	Adult	Multi-tissue pectoral and pelvic fins	Blastema-mediated cell proliferation, chondrogenesis, myogenesis	Conant, 1970, 1972; Nogueira et al., 2016
Salamander (Urodela/ Caudata)	Possibly most species	Adult and juvenile	Multi-tissue tail, including spinal cord	Blastema-mediated cell proliferation, axonogenesis, angiogenesis, chondrogenesis, myogenesis	Egar and Singer, 1972; Iten and Bryant, 1976; O'Hara et al., 1992; Schnapp et al., 2005; Vincent et al., 2015
	Possibly most species	Adult and juvenile	Multi-tissue limbs, including muscle and skeleton	Blastema-mediated cell proliferation, axonogenesis, angiogenesis, chondrogenesis, myogenesis	Scadding, 1977; Gardiner and Bryant, 2007; Kragl et al., 2009; Garza-Garcia et al., 2010
	Axolotl (*Ambystoma mexicanum*)	Adult and juvenile	Heart (ventricle)	De-differentiation, organ-wide and blastema-mediated cell proliferation, myogenesis, angiogenesis	Flink, 2002; Vargas-Gonzalez et al., 2005; Cano-Martínez et al., 2010
	Eastern spotted newt (*Notopthalmus viridescens*)	Adult	Heart (ventricle)	De-differentiation, organ-wide and blastema-mediated cell proliferation, myogenesis, angiogenesis	Laube et al., 2006; Witman et al., 2011; Mercer et al., 2013
	Axolotl (*Ambystoma mexicanum*)	Adult	Skin	Re-epithelization, cell proliferation	Slack, 1980; Seifert et al., 2012b
	Eastern spotted newt (*Notopthalmus viridescens*)	Adult	Eye lens	De-differentiation (transdifferentiation), cell proliferation	Tsonis et al., 2004; Eguchi et al., 2011; Sousounis et al., 2013
Anura	African clawed frog (*Xenopus laevis*); African (Zaire) dwarf clawed frog (*Hymenochirus bottgeri*)	Tadpole	Multi-tissue limbs, including muscle and skeleton	Blastema-mediated cell proliferation, axonogenesis, angiogenesis, chondrogenesis, myogenesis	Amaya, 2005; Suzuki et al., 2006; Vickaryous and Olsen, 2007
	African clawed frog (*Xenopus laevis*)	Tadpole	Multi-tissue tail, including spinal cord	Re-epithelialization, blastema-mediated cell proliferation, axonogenesis, ependymal tube outgrowth, neurogenesis, angiogenesis, chondrogenesis, myogenesis	Ryffel et al., 2003; Gargioli and Slack, 2004; Chen et al., 2006; see also Mochii et al., 2007
	African clawed frog (*Xenopus laevis*)	Tadpole, froglet	Skin	Re-epithelialization, blastema-mediated cell proliferation, angiogenesis	Yokoyama et al., 2011; Bertolotti et al., 2013

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Table 1. Continued

Taxon	Species	Life stage	Tissue/organ	Mechanism(s)	Source
Mammalia	Spiny mice (*Acomys cahirinus*, *A. kempi*, *A. percivali*); New Zealand white rabbit (*Oryctolagus cuniculus*)	Adult	Ear pinna	Re-epithelialization, blastema-mediated cell proliferation, axonogenesis, chondrogenesis	Williams-Boyce and Daniel, 1986; Gawriluk et al., 2016; Santos et al., 2014
	Spiny mice (*Acomys kempi*, *A. percivali*)	Adult	Skin	Re-epithelization, cell proliferation, hair follicle neogenesis	Seifert et al., 2012a
	Laboratory mouse (*Mus musculus*); humans (*Homo sapiens*)	Neonate, juvenile and adult	Multi-tissue digit tip (distal third of third phalangeal element)	Blastema-mediated cell proliferation, axonogenesis, angiogenesis, chondrogenesis	Fernando et al., 2011; Rinkevich et al., 2011; Simkin et al., 2015; Shieh and Cheng, 2015
Lepidosauria (tuatara and lizards)	Tuatara and many species of lizards, including virtually all gekkotans (e.g. *Eublepharis macularius*, *Gekko japonicas*), as well as various lacertids (e.g. *Podarcis hispanicus*), dactyloids (e.g. *Anolis carolinensis*) and others	Adult	Multi-tissue tail, including spinal cord	Blastema-mediated cell proliferation, axonogenesis, angiogenesis, chondrogenesis, myogenesis, osteogenesis, lymphangiogenesis	Arnold, 1984; Alibardi, 1995; Daniels et al., 2003; Blacker et al., 2007; McLean and Vickaryous, 2011, Delorme et al., 2012; Hutchins et al., 2014; Liu et al., 2015; Lozito and Tuan, 2015, 2016, 2017; Payne et al., 2017
	Wall geckos (*Tarentola annularis*, *T. mauritanica*); slow worm (*Anguis fragilis*)	Adult	Osteoderms (bones) within the skin of the regenerated tail	Osteogenesis	Bryant and Bellairs, 1967; Vickaryous et al., 2015
	Various (10+) genera of gekkotans (including *Ailuronyx tachyscopaeus*, *Eublepharis macularius*, *Geckolepis magalepis*), dactyloids (*Anolis carolinensis*) and scincids	Adult	Skin	Re-epithelialization, cell proliferation, angiogenesis, fibrogenesis	Bauer et al., 1989; Wu et al., 2014; Peacock et al., 2015; Scherz et al., 2017
	Iberian wall lizard (*Podarcis hispanicus*); Gallot's lizard (*Gallotia galloti*)	Adult	Brain (telencephalon)	Neurogenesis	Font et al., 1991, 1997; Romero-Alemán et al., 2004
	Common wall lizard (*Podarcis muralis*)	Adult	Articular cartilage of the knee (stifle)	Chondrogenesis	Alibardi, 2015, 2016
	Ornate dragon lizard (*Ctenophorus ornatus*)	Adult	Optic nerve	Axonogenesis	Beazley et al., 1997, 2003; Dunlop et al., 2004

1997). However, as for most groups, the full repertoire of regenerative capabilities – especially those not readily observed in the wild (e.g. regeneration of the forebrain and optic nerve) – almost certainly remains underappreciated.

A second advantage of using lizards in regeneration research is that tissues of the tail (including blood vessels, lymphatics and the spinal cord) can be easily accessed, manipulated and studied *in vivo*, with minimal consequence to the remainder of the body. For example, the spinal cord of the tail – which closely resembles that of the mammalian body – can be transected and experimentally altered without the risk of limb paralysis or incontinence (Whimster, 1978; Szarek et al., 2016). Similarly, the lizard tail has been used as a novel platform to investigate lymphangiogenesis without impairing lymphatic drainage to the body core or limbs (Daniels et al., 2003; Blacker et al., 2007).

In addition, regeneration in lizards is often paired with structural adaptations that minimize tissue damage and facilitate recovery. In the laboratory, these structural adaptations can be exploited to initiate survivable (and arguably less invasive) traumas. For example, at least 10 unrelated genera of lizards can partially avulse (detach) the skin to escape capture, a phenomenon known as regional integumentary loss (Bauer et al., 1989; Bauer and Russell, 1992; Scherz et al., 2017) (Fig. 1A). Thus, simply grasping or handling the lizard is often sufficient to create non-lethal skin wounds of considerable size (Fig. 1A). A more widespread and yet equally impressive form of avoiding predation is tail loss or caudal autotomy (see Glossary). In response to the threat or act of confrontation, many (but not all) lizards – including some of the most species-rich clades such as geckos (1650 species) and skinks (1598 species) – are able to voluntarily self-sever or autotomize a portion of their tail (Fig. 1B,C). In the laboratory, autotomy can be achieved by pinching or twisting the tail, obviating the need for surgical amputation. Both regional integumentary loss and caudal autotomy are associated with pre-existing planes of weakness in the tissues, which permit controlled rupturing, as well as the ability to vasoconstrict adjacent blood vessels to minimize hemorrhaging (Bellairs and Bryant, 1985; Schubert and Christopher, 1985; McLean and Vickaryous, 2011; Sangaard et al., 2012).

Of further benefit to their use in research, many lizard species are common in the pet trade and, as such, are commercially bred and widely available. Some, including *Anolis carolinensis* (the green or Carolina anole) and *Eublepharis macularius* (the leopard gecko), have well-established husbandry practices (e.g. Sanger et al., 2008; Vickaryous and McLean, 2011) and are tolerant of anesthesia and surgery (Delorme et al., 2012; Lozito and Tuan, 2016; Szarek et al., 2016).

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Journal of Experimental Biology (2017) 220, 2858-2869 doi:10.1242/jeb.126862

GLOSSARY

Appositional growth
Surface or external growth.
Articular cartilage
Cartilage of joint surfaces, characteristically smooth and lacking a perichondrium (fibrous outer covering).
Autotomy
A reflexive self-detachment mechanism associated with pre-existing structural adaptations that minimize trauma to adjacent tissues.
Blastema
An accumulation of proliferating, mesenchymal-like cells that gives rise to new tissues. Evidence from various non-lizard species indicates that blastema cells are a heterogeneous population of lineage-restricted progenitor cells.
Endochondral ossification
Bone deposition that replaces a cartilaginous template.
Epiphyseal growth plate
The interval of a long bone where growth and remodelling takes place. Located between the shaft (diaphysis) and the ends of the bone with the joint surfaces (epiphyses).
Interstitial growth
Growth from within, via internal cell division.
Neurogenesis
The generation of new neurons from a progenitor population.
Radial glia
Neuronal progenitor cells located at the ventricular surface of the brain. Characterized by a lengthy apical process and the expression of markers otherwise common to glial (neuronal support) cells.
Re-epithelialization
Migration and proliferation of keratinocytes to restore the stratified architecture of the epidermis.
Regeneration
An injury-mediated, tissue-specific reparative program. Often involves the formation of a blastema.
Scar tissue
A permanent, non-specific (fibrous) replacement tissue.

Furthermore, annotated genomes have been published for an ever-increasing number of lizard species, including *A. carolinensis* (Alföldi et al., 2011), *E. macularius* (Xiong et al., 2016) and *Gekko japonicas*, Schlegal's Japanese gecko (Liu et al., 2015). Perhaps not surprisingly, comparative genomic and transcriptomic analyses of these taxa reveal enriched expression of genes associated with wound healing (e.g. platelet derived growth factor receptor alpha, *pdgfrα*), cell proliferation (e.g. prostacyclin synthase, *PTGIS*) and tissue morphogenesis (e.g. *PAX7* and *col2a1*) (Hutchins et al., 2014; Liu et al., 2015).

Finally, lizards are amniotes, and are thus more closely related to mammals than other common models of regeneration such as zebrafish and axolotls. As such, they not only expand the comparative framework of regeneration-competent species, but also offer insight into the evolution (and widespread loss) of reparative capacities in mammals. Furthermore, lizards are one of the largest and most diverse groups of terrestrial vertebrates. More than 6100 species are currently recognized (Uetz et al., 2016; compared with ∼5400 mammals), encompassing a wide range of morphologies (including limbless species), body sizes (ranging in adult body length from ∼1.6 to >300 cm; Hedges and Thomas, 2001; Laver et al., 2012) and locomotory behaviours (including bipedal running, swimming, burrowing and even gliding). Hence, as a group, lizards provide an excellent platform to probe questions related to the biology of regeneration. These include the relationships between regeneration and ecology or morphology, and whether regeneration is always an adaptive trait (Bely and Nyberg, 2010).

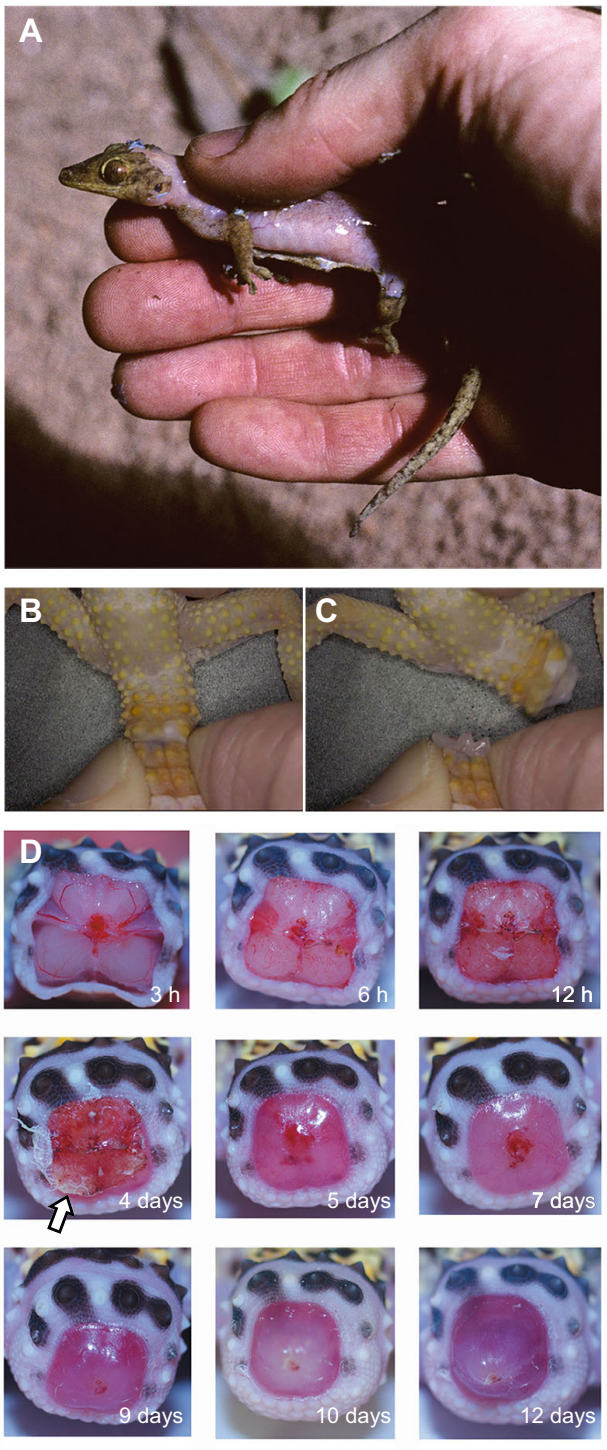

Fig. 1. Avoiding predation via self-mutilation. To escape potential predators – including humans – some species of lizard can traumatically detach portions of their skin (A) or their tail (B,C). Damaged tissues undergo scar-free wound healing and, over a period of one or more months, tissue regeneration (D). (A) Attempting to evade capture, *Ailuronyx tachyscopaeus* (dwarf bronze gecko) has undergone regional integumentary loss. Sloughing of the skin reveals the exposed deep dermis. Over time, the missing skin will be regenerated. Reproduced with the kind permission of Henrik Bringsøe (www.natureswindow.dk). (B–D) As demonstrated by *Eublepharis macularius* (leopard gecko), tail regeneration is spontaneously initiated following autotomy. The site of tail loss is rapidly capped by a protective clot, deep underneath which a wound epithelium begins to form. Once complete, the clot is lost (white arrow) and the replacement tail emerges and continues to grow.

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Caudal autotomy: release, regenerate, repeat

Autotomy is a reflexive self-amputation mechanism that ruptures the spinal cord, peripheral nerves, blood and lymphatic vessels, as well as the skeleton, tail musculature and adipose tissue (Fig. 1D). The autotomized tail then acts as a decoy, distracting the predator by vigorously moving about, while the otherwise intact lizard escapes (Arnold, 1984; Higham et al., 2013). Although most commonly associated with lizards, the phenomenon of tail autotomy is also practiced by various other reptiles, including *Sphenodon punctatus* (the tuatara, a superficially lizard-like species endemic to New Zealand; Seligmann et al., 2008), some snakes (Arnold, 1984; Slowinski and Savage, 1995) and many amphisbaenians (a group of burrowing, worm-like species; Gans, 1978). Outside of reptiles, autotomy has also been reported for plethodontid salamanders (Wake and Dresner, 1967; Dawley et al., 2012) and even some rodents (McKee and Adler, 2002). Interestingly, whereas the tuatara, plethodontid salamanders and most lizards can regenerate the tail following autotomy, snakes, amphisbaenians and rodents cannot.

To facilitate autotomy and minimize tissue damage to the retained tail stump, most lizards (as well as the tuatara, amphisbaenians and possibly some snakes) have evolved fracture planes (Arnold, 1984; Bellairs and Bryant, 1985). Fracture planes are connective tissue partitions that pass transversely between segments of dermis, muscle and adipose tissue, subdividing individual tail vertebra into cranial and caudal components (Fig. 2A) (McLean and Vickaryous, 2011; Sangaard et al., 2012; Lozito and Tuan, 2017). During this intravertebral form of autotomy, the fracture plane is split and the intervening vertebra is broken. Blood loss is minimized by the action of thick, smooth muscle sphincters located on the major arterial supply to the tail (the caudal artery). Once the tail is detached, the sphincter immediately proximal to the site of tail loss is constricted (McLean and Vickaryous, 2011). Significantly, tail autotomy is repeatable, provided that the remaining stump of the original tail still has fracture planes. Therefore, a given individual is capable of losing its tail more than once. Alternatively, and less commonly, some lizards (as well as plethodontid salamanders, rodents and most tail-autotomizing snakes; Arnold, 1984; McKee and Adler, 2002) employ intervertebral autotomy, whereby the tail is lost at locations between individual vertebrae. At least in lizards, intervertebral autotomy does not appear to correlate with any specific anatomical modifications (Arnold, 1984).

For most species, tail autotomy is paired with the spontaneous process of tail regeneration (Fig. 1D). As an injury-mediated event, tail regeneration begins with the formation of a temporary seal or a clot of tissue exudate and blood. Beneath the developing clot, epidermal cells (keratinocytes) at the wound margins begin to proliferate (McLean and Vickaryous, 2011; Gilbert et al., 2013a). As they spread across the wound site they secrete matrix metalloprotease 9 (MMP9), a protease, to cut a pathway through the damaged tissue, essentially resurfacing the wound site (Delorme et al., 2012; Lozito and Tuan, 2017). Below this neo- or wound epithelium, an aggregation of proliferating mesenchymal-like cells – the blastema (see Glossary) – appears. Similar to zebrafish (Jaźwińska et al., 2007) and axolotls (Lévesque et al., 2007), the ongoing regenerative program is mediated in part by members of the transforming growth factor beta (TGFβ) family, including TGFβ1, TGFβ3 and *activin-βA* (Delorme et al., 2012; Gilbert et al., 2013b). Prior to their differentiation, blastema cells also express the cytokine vascular endothelial growth factor A (VEGF; Payne et al., 2017). Over a period of days to weeks, new tissues (including blood and lymphatic vessels, skeletal muscle, adipose tissue, cartilage, peripheral nerves and a spinal cord) replace the once-cellular blastema (Daniels et al., 2003; McLean and Vickaryous, 2011; Delorme et al., 2012; Lozito and Tuan, 2017). The result is a functional regenerate tail that closely resembles, but does not replicate, the original. The major differences in the regenerate anatomy include: the replacement of the bony vertebral column with an unsegmented cone of cartilage (Fig. 2A); the absence of grey matter in the spinal cord; and the absence of fracture planes in the new tail. Despite the obvious convenience of the autotomy–regeneration relationship, it is worth noting that the two events are, in fact, independent. As has been experimentally demonstrated, tails regenerate equally well following either tail autotomy at the fracture plane or surgical tail amputation outside the fracture plane (Delorme et al., 2012; Lozito and Tuan, 2017).

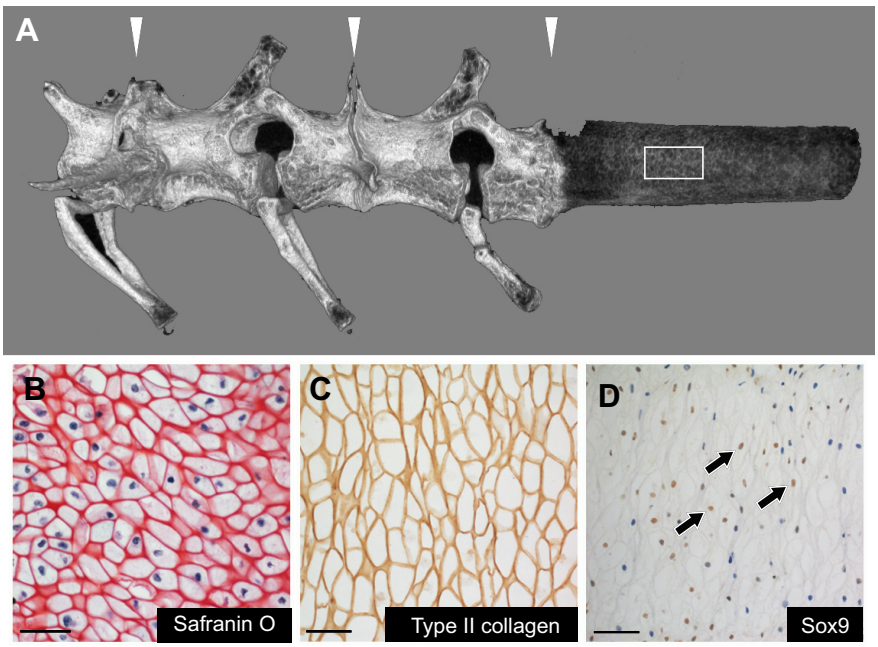

Fig. 2. Skeletal 'tales'. Following autotomy, the regenerated skeleton of the tail clearly differs from that of the original. (A) Microcomputed tomographic reconstruction of the tail skeleton of *Gekko gecko* (Tokay gecko). Whereas the original tail consists of multiple bony vertebrae (left), the regenerate skeleton is an unsegmented hollow cone of cartilage (right) (adapted from Gilbert et al., 2013a). As for most tail-autotomizing species, self-severing of the original tail is facilitated by intravertebral fracture planes (arrowheads). (B–D) The regenerate skeleton of *Eublepharis macularius* (leopard gecko) is rich in glycosaminoglycans (B; staining with Safranin O) and type II collagen (C). In addition, resident cells of the cartilaginous cone express the transcription factor SOX9 (D; black arrows), often identified as the 'master regulator' of chondrogenesis. Scale bars, 20 μm.

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Tails of cartilage

Whereas the original lizard tail is supported by a series of bony vertebrae, the regenerate appendage replaces these elements with an unsegmented and hollow cone of cartilage; individual vertebrae are never reformed (Alibardi, 1995; McLean and Vickaryous, 2011; Lozito and Tuan, 2015) (Fig. 2). This ability to produce abundant cartilage stands in stark contrast to the mammalian condition, where cartilage repair and generation during adulthood is limited at best. Similar to cartilage development during vertebrate embryogenesis, cartilage regeneration in lizards begins when mesenchymal-like cartilage progenitor (chondroprogenitor) cells aggregate to form a condensation. As these chondroprogenitors differentiate, they begin to deposit an ECM rich in the quintessential building blocks of cartilage: glycosaminoglycans and the fibril protein type II collagen (Alibardi, 1995; Lozito and Tuan, 2015) (Fig. 2B,C). Cartilage development and regeneration are also similar in that cartilage cell (chondrocyte) differentiation is marked by expression of the transcription factor SOX9 (Fig. 2D), frequently characterized as the 'master regulator' of chondrogenesis (Kozhemyakina et al., 2015). However, unlike embryonic chondrogenesis, ECM deposition occurs before the onset of SOX9 expression during cartilage regeneration (McLean and Vickaryous, 2011). These findings suggest that injury-mediated cartilage formation is not a simple recapitulation of the original developmental program. And while both modes of chondrogenesis involve a combination of appositional and interstitial growth (see Glossary; Alibardi, 1995), the regenerated tissue is uniquely cell-rich, with a low ECM to cell volume ratio.

In addition to demonstrating a cell-rich architecture, chondrocytes of the regenerated tail are distinctly enlarged (Fig. 2B–D). During mammalian limb development, enlarged or hypertrophic chondrocytes are a transient cell type. As the limb grows, this hypertrophic cartilage is eroded and replaced by bone, a process known as endochondral ossification (see Glossary). In contrast, the enlarged chondrocytes of the regenerate lizard tail are almost entirely permanent (Alibardi, 1995; McLean and Vickaryous, 2011; Lozito and Tuan, 2015). The only exception is a small population located immediately adjacent to the original vertebral skeleton. As revealed by recent investigations using *A. carolinensis*, these cells express various markers associated with endochondral ossification, including bone morphogenetic protein-6 (BMP-6) and the morphogen Indian hedgehog (Ihh) (Lozito and Tuan, 2015). Once the new tail has formed, these chondrocytes are replaced by several millimetres of bone, anchoring the original skeleton to the new. Interestingly, this bony anchor appears to have a different origin than the regenerated (cartilaginous) skeleton. Whereas the permanently cartilaginous cone originates from progenitor cells in the blastema, the bony anchor is derived exclusively from cells residing within the periosteum of the original tail vertebrae (Lozito and Tuan, 2016).

The capacity to generate permanent cartilage in response to injury may not be restricted to the tail. For example, it has been reported that *Podarcis muralis* (the common wall lizard) is able to restore articular cartilage (see Glossary) following excisional injuries to the knee (Alibardi, 2015, 2016). As evidenced by cell tracking experiments and telomerase expression, chondroprogenitor populations located at the surfaces of articular cartilage are activated in response to injury (Alibardi, 2015, 2016). In conjunction with resident chondroblasts of the epiphyseal growth plate (see Glossary) at the knee, these chondroprogenitors proliferate and ultimately restore the damaged articular cartilage within a period of weeks (Alibardi, 2015).

Neurogenesis, axonogenesis and the ependymal tube: restoring the nervous system

Restoring the spinal cord in the regenerated tail

Tail regeneration involves not only outgrowth of the cartilaginous skeleton, but also the re-establishment of the spinal cord. In lizards (as well as salamanders), the spinal cord passes from the base of the brain to almost the tip of the tail. In contrast, amongst mammals, the spinal cord terminates cranial to the pelvis and never enters the tail. Along its entire length, the lizard spinal cord demonstrates a conserved morphology, essentially identical to that of mammals: a central canal (continuous with the ventricular system of the brain) encircled by a sleeve or tube of ependymal cells, surrounded by grey matter (neuronal cell bodies) and white matter (nerve tracks) (Fig. 3A). At regular intervals, the spinal cord is flanked by dorsal root ganglia and spinal nerves. During tail autotomy, the spinal cord and spinal nerves are severed. Within days, outgrowth of the regenerate spinal cord begins as ependymal cells near the site of rupture first proliferate and then assemble into the tube-like structure enclosing the central canal (McLean and Vickaryous, 2011). Ependymal tube outgrowth is closely matched by axonogenesis, the regrowth of severed axons. Newly formed nerve tracts originate from dorsal root ganglia in the remaining tail stump and descending tracts from the white matter of the original spinal cord (Bellairs and Bryant, 1985) (Fig. 3B). Conspicuously, the regenerated spinal cord does not contain grey matter, nor is there any restoration of dorsal root ganglia in the new tail; all the replacement innervation appears to originate from more proximal neuronal structures (Bellairs and Bryant, 1985). Although this stands in stark contrast to the situation in salamanders, wherein the spinal cord and dorsal root ganglia are near-perfectly replaced during tail regeneration (Mchedlishvilli et al., 2012), it is worth noting that the regenerated lizard tail is fully functional (Arnold, 1984; Bellairs and Bryant, 1985). Like the original appendage, if regenerated tails are autotomized, they too are capable of vigorous independent movements to distract predators (Meyer et al., 2002).

Neurogenesis in the lizard brain

Physiological neurogenesis

It is now widely recognized that all adult vertebrates can generate new neurons, a process known as physiological neurogenesis (see Glossary; Kaslin et al., 2008). In mammals, physiological neurogenesis is restricted to two discrete areas: the subventricular zone (SVZ) of cerebral cortex and the subgranular zone of the dentate gyrus (Kaslin et al., 2008). However, for many non-mammalian vertebrates, including teleost fish (Kizil et al., 2012; Zupanc, 2001), salamanders (Maden et al., 2013), various birds (Alvarez-Buylla et al., 1994) and lizards (e.g. Perez-Cañellas and García-Verdugo, 1996; Marchioro et al., 2005; see Font et al., 2001), physiological neurogenesis routinely occurs within many areas of the brain. Among lizards, these neurogenic areas include several regions of the telencephalon (e.g. dorsal and lateral cerebral cortex, anterior dorsal ventricular ridge, nucleus sphericus), as well as the olfactory bulb and cerebellum (Font et al., 2001). However, physiological neurogenesis is best understood for the medial (cerebral) cortex (Fig. 3C–E), the equivalent of the mammalian dentate gyrus (and likely involved in place learning and relational memory; see Naumann et al., 2015). New neurons are generated a short distance away from the medial cortex, in the adjacent ventricular zone (VZ). The VZ is a pseudostratified epithelium that lines the ventricular system of the brain (Fig. 3D,E). Although the VZ of reptiles is distinct from the better-known SVZ of mammals, the two regions appear to serve similar roles as

Journal of Experimental Biology (2017) 220, 2858-2869 doi:10.1242/jeb.126862

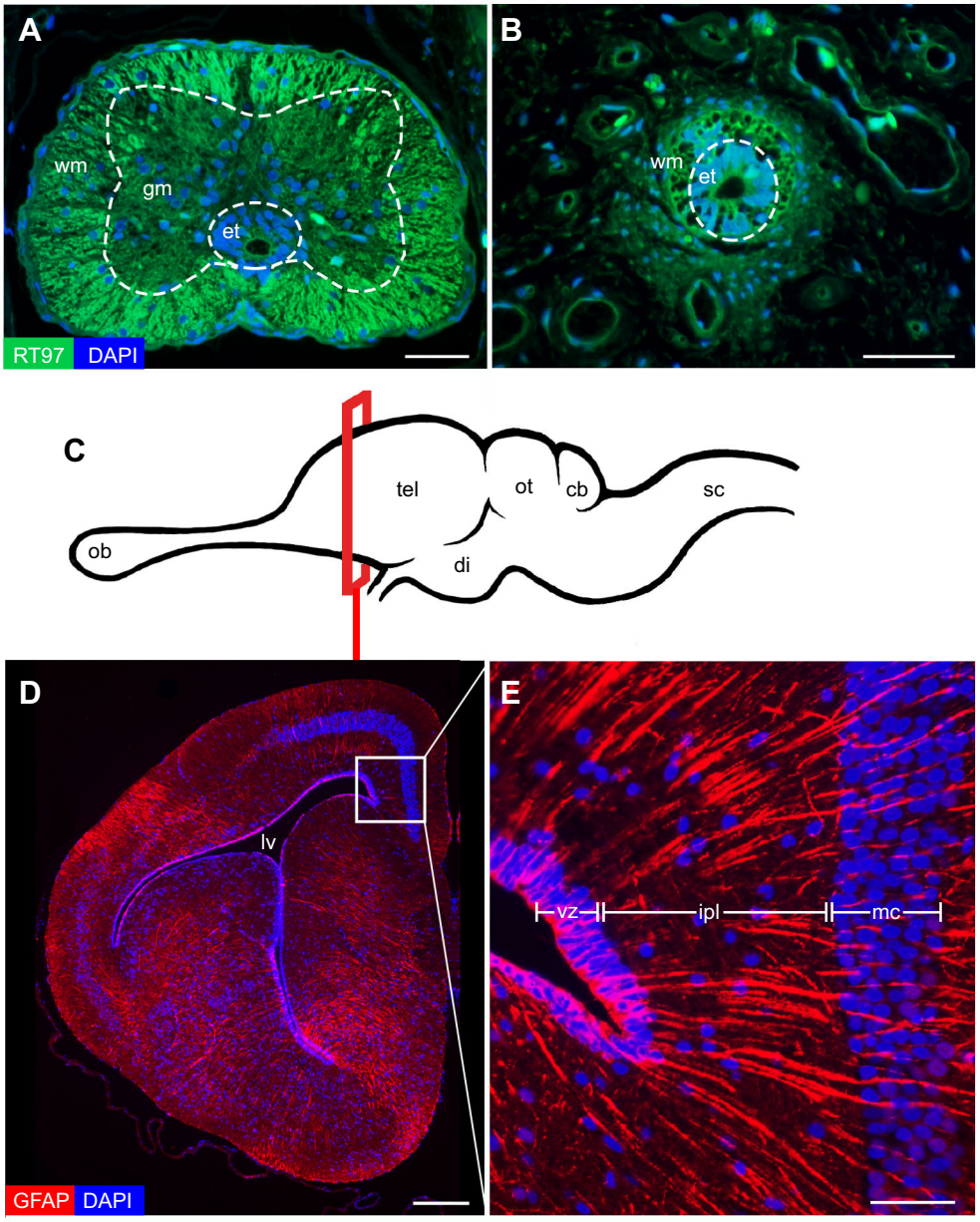

Fig. 3. Renewing the nervous system. Although tail-autotomizing lizards such as *Eublepharis macularius* (leopard gecko) can restore the spinal cord during tail regeneration, the replacement lacks the fidelity of the original. (A) As for other lizards, the original spinal cord of the tail consists of a tubular arrangement of ependymal cells (enclosing the central canal), surrounded by grey matter (invested with neuronal cell bodies) and white matter (nerve tracts labelled by RT97). (B) The fully regenerated spinal cord includes the ependymal tube and white matter, but conspicuously lacks grey matter. (C) Schematic illustration of a leopard gecko brain. (D) A representative transverse section through the left telencephalon. (E) Radial glia (labelled here with GFAP) within the ventricular zone serve as the self-renewing source of new neurons, and provide scaffolds for neuroblast migration. Once neuroblasts arrive in the cellular layer of the medial cortex, they become neurons. Abbreviations: cb, cerebellum; DAPI, 4′-6-diamino-2-phenylidole (nuclear marker); di, diencephalon; et, ependymal tube; GFAP, glial fibrillary acid protein (radial glia cell marker); gm, grey matter; ipl, inner plexiform layer; lv, lateral ventricle; mc, medial cortex; ob, olfactory bulb; ot, optic tectum; sc, spinal cord; RT97, neurofilament marker; tel, telencephalon; vz, ventricular zone; wm, white matter. All scale bars, 10 μm (except D, 50 μm).

proliferative neurogenic niches (García-Verdugo et al., 2002; Kaslin et al., 2008). The main cell types residing within the VZ are ependymal cells and radial glia (see Glossary; also called ependymoradial glia). Radial glia are generally accepted as the precursor or source population of new neurons (Delgado-Gonzalez et al., 2011). The most likely scenario is that radial glia within the VZ undergo asymmetrical cell division, thereby self-renewing and giving rise to a migratory daughter cell or neuroblast. Neuroblasts then travel into the cortices to differentiate, and become structurally mature (and presumably fully functional) neurons.

Whereas physiological neurogenesis may be a relatively common phenomenon among lizards, evidence indicates that, at least in some species, it is seasonally variable (a phenomenon also reported for songbirds; Brenowitz and Larson, 2015). For example, neurogenesis associated with the olfactory system of *Gallotia galloti* (Gallot's lizard) demonstrates a significant decrease in the number of neuroblasts migrating to the olfactory bulbs during the summer (Delgado-Gonzalez et al., 2011). Based on these observations, it is possible that *G. galloti* exhibits a corresponding seasonal fluctuation in olfactory abilities – an intriguing prediction that deserves further investigation. The same study also reported that the time frame for the completion of neurogenesis was much longer in *G. galloti* (90 days) than for other species (e.g. 7 days in *Podarcis hispanicus*, the Iberian wall lizard; Lopez-Garcia et al., 1990). Whether this comparative delay reflects species-specific variation or is the result of differences in (for example) the chronological age of the experimental animals (the *G. galloti* studied were ∼6 years old; the age of *P. hispanicus* was not specified) remains uncertain (Molowny et al., 1995; Delgado-Gonzalez et al., 2011).

Compensatory neurogenesis

In addition to constitutive neurogenesis, at least some teleost fish, salamander and lizard species are also proficient at generating new neurons in response to brain injuries, so-called compensatory neurogenesis (Font et al., 1991, 1997; Kizil et al., 2012; Maden et al., 2013). In lizards, the antimetabolite 3-acetylpyridine (3AP, a

nicotinamide antagonist) has been used to chemically target neurons in the cellular layer of the medial cortex. Using *P. hispanicus*, a single treatment with 3AP causes 34–97% of the neurons in the medial cortex to undergo apoptosis (Font et al., 1991, 1997). Treated lizards quickly develop a suite of behavioural changes consistent with neurotoxicity, as well as problems with spatial memory performance and capturing prey (although not with walking or eating; Font et al., 1991, 1997). Within 10 days following treatment, the behavioural impairments are no longer obvious, and by 42–49 days post-treatment the populations of neurons within the medial cerebral cortex appear to be almost restored. Curiously, while compensatory neurogenesis restores the heavily lesioned medial cerebral cortex within 7 weeks, restoration of neurons to an adjacent area (the dorsomedial cortex), which by comparison is only modestly damaged by 3AP treatment, is more variable (Font et al., 1997).

Building on these findings, the capacity for compensatory neurogenesis to repair a physical lesion (an incision to the dorsal cortex) has also been explored in *G. galloti* (Romero-Alemán et al., 2004). Within days, proliferating immune cells of the central nervous system (microglia and macrophages) are observed at the wound site. In the following 2–4 weeks, proliferation is additionally upregulated at the VZ adjacent to the injury. This marked increase in proliferation persists for 240 days, suggesting ongoing tissue restoration, though immune cells return to baseline numbers during this time. To date, the full extent to which the lizard brain can regenerate from a direct physical lesion is unclear.

Restoring the optic nerve

Another region of the central nervous system demonstrating variable responses to injury is the optic nerve. The optic nerve consists of axons from retinal ganglion cells, which integrate and relay visual information from the retina of the eye to visual centres in the brain (Fischer and Leibinger, 2012; Wang et al., 2012). In mammals and birds, damage to these axons can result in vision loss, as retinal ganglion cells degenerate and undergo cell death (Lang et al., 1998, 2017; Williams, 2017). Cellular degeneration and the inability to restore the visual pathway in these species appears to be the result of a complex inhibitory microenvironment, related to the formation of a glial scar (rich in proteoglycans and glial cells) and various axon-impeding proteins such as Nogo-A (Dunlop et al., 2004; Lang et al., 2017). As might be expected, species capable of restoring vision after injury to the optic nerve (e.g. zebrafish) are characterized by retinal ganglion cell survival (Zou et al., 2013), and the absence of axon inhibitory proteins such as Nogo (Abdelesselem et al., 2009) and a glial scar (Bollaerts et al., 2017). Paradoxically, the optic nerve of some lizard species can regenerate, even though they express Nogo-A and form a glial scar (Lang et al., 1998, 2017). Optic nerve regeneration is particularly efficient in *Ctenophorus ornatus* (the ornate dragon lizard), with the crushed optic nerve outgrowing to re-contact the optic tectum within 1 month (Beazley et al., 1997; Dunlop et al., 2004). Although excitatory and inhibitory neurotransmission is dysfunctional following regeneration, and vision is not spontaneously returned, lizards can regain sight with training (Beazley et al., 2003). One explanation, based on *in vitro* experiments, is that retinal ganglion cells of lizards are insensitive to the inhibitory signals that otherwise obstruct mammalian axon outgrowth. Using an explant strategy, mammalian (rat) dorsal root ganglia and lizard (Gallot's lizard) retina were cultured on each of mammalian and lizard glial cells. Whereas both these environments inhibited regrowth of mammalian axons, neither inhibited the regrowth of lizard axons (Lang et al., 1998). Combined, these data reveal a surprising diversity across vertebrates in how the optic nerve responds to injury, with lizards uniquely interposed between full functional restoration and regenerative failure.

Skin, scales and scarless: an emerging model of scar-free healing

The evolutionary success of reptiles has often been linked to their skin, and the crucial roles it plays in preventing water loss and resisting mechanical abrasions. Reptile skin is characterized by the presence of scales – low-relief integumentary appendages composed of a superficial, heavily keratinized epidermis capping a deeper core of dermis. In addition to nerves and blood vessels, the dermis also houses pigment cells and, in some species, small bone-rich organs known as osteoderms. Remarkably, in some osteoderm-bearing species (such as *Tarentola annularis*, the white-spotted wall gecko) these small bones are redeveloped during tail regeneration (Vickaryous et al., 2015).

Among lizards, the fidelity of the reparative response to skin injuries varies both taxonomically and with location of the injury. Arguably, the most vivid example of skin regeneration occurs following regional integumentary loss, the ability to partially avulse (traumatically detach) the skin to escape capture (Bauer et al., 1989; Bauer and Russell, 1992; Scherz et al., 2017) (Fig. 1A). While the entire epidermis and up to 90% of the dermis is initially sloughed off, over time the site of mutilation is completely restored (Bauer et al., 1989; Bauer and Russell, 1992). A similar mode of skin shedding (~60% of total dorsal body surface area) and subsequent regeneration has also been documented in spiny mice (*Acomys* spp.) (Seifert et al., 2012a).

Beyond those species capable of regional integumentary loss, the ability of lizards to regenerate the skin is highly variable. Some, such as *E. macularius*, can restore both scalation and pigmentation following excisional (surgically mediated) wounds to the skin of the tail and body (Peacock et al., 2015) (Fig. 4). Others, such as *Iguana iguana* (green iguana), cannot (Wu et al., 2014). Curiously, *A. carolinensis* can restore scales following excisional wounds to the tail but not the body, and the original skin coloration is not restored at either wound location (Wu et al., 2014). These data indicate that scar-free cutaneous repair is not a universal trait of lizards. As a result, future studies comparing scar-free and scar-forming species would provide excellent opportunities to unravel the factors and mechanisms necessary to permit and promote healing.

Cutaneous wound healing involves a complex series of overlapping events. While the events themselves are essentially conserved among all species (including those that form scars and those that do not), their magnitude, timing of onset and duration vary based on the mode of wound healing (e.g. Seifert et al., 2012b; Peacock et al., 2015). For example, restoration of the epidermis, or re-epithelization, is necessary to re-establish the barrier functions of the skin. Whereas this process may take 1–2 weeks in a scarring mammalian wound, a comparable cutaneous injury in *E. macularius* re-epithelizes within 5 days (Peacock et al., 2015). Comparable rates of re-epithelization have also been reported for other scar-free wound healing species, including axolotls and African spiny mice (Seifert et al., 2012a,b). Another key reparative event is collagen deposition within the wound bed. Not only is the rate of collagen deposition in scar-free wound healing slower than that of scarring wounds, but the resulting matrix architecture differs. Scars are characterized by parallel bundles of collagen, whereas scar-free healing recreates the basket-weave organization of the original uninjured dermis (Ferguson and O'Kane, 2004; Corr et al., 2009; Peacock et al., 2015).

Journal of Experimental Biology (2017) 220, 2858-2869 doi:10.1242/jeb.126862

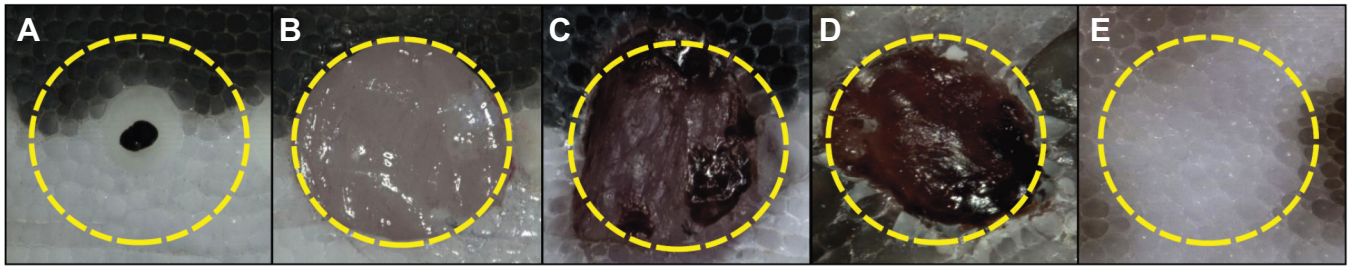

Fig. 4. Scaly and scar-free. Recent studies have determined that some lizard species are capable of healing wounds to the skin on both the tail and body without scarring. (A) The dorsal skin of *Eublepharis macularius* (leopard gecko) consists of a regular pattern of small scales arranged in a rosette around larger tubercular scales (marked with a black dot). (B) A 3 mm full-thickness cutaneous biopsy (yellow hatched lines) that removes both the epidermis and dermis is created, thus exposing the underlying muscle. (C) At 2 days post-biopsy, a clot has formed. (D) Although the wound looks unchanged at 8 days post-biopsy, re-epithelization is complete beneath the clot. (E) By 45 days post-biopsy, the skin has regenerated, complete with scalation and pigmentation. Curiously, the large tubercular scales are not restored. Note that the pattern of pigmentation across the body, including around the wound site, normally changes over time.

Another striking difference between scar-free and scar-forming models is the integrity and the abundance of blood vessels present within the wound bed. Scarring species are characterized by the rapid and transient formation of granulation tissue within the wound. Granulation tissue is an infill matrix with a vascular density double that of the uninjured dermis (Bluff et al., 2006). In addition, these newly formed vessels are typically disorganized and structurally immature, lacking perivascular support (Gurtner et al., 2008; Bertolotti et al., 2013; Bluff et al., 2006). In contrast, when *E. macularius* heal cutaneous wounds (Peacock et al., 2015) or when they regenerate their tails (Payne et al., 2017), new blood vessels are typically reinforced by vascular smooth muscle cells, and their overall abundance never exceeds that of the surrounding uninjured tissue.

Conclusions

Lizards are highly capable regenerators, demonstrating an inventory of reparative abilities far greater than any other amniote. These include a celebrated capacity to replace the tail, complete with a regenerated spinal cord and cartilage, as well as being able to rebuild areas of the skin and even portions of the brain. Notwithstanding their exotic reputation, several lizard species have proven to be both versatile and tractable laboratory models. In the laboratory, their ability to autotomize the tail (and for some species, spontaneously slough the skin) provides a naturally evolved, easily performed and highly tolerated alternative to amputation or surgical excision. Furthermore, the lizard tail provides a natural demonstration that perfect replication is biologically unnecessary for functional restoration.

While work to date has revealed that many mechanisms and cellular participants involved in wound healing and regeneration in lizards are conserved with those of salamanders and teleosts (and even some mammals) numerous questions remain. For example, how do lizards prevent (or at least limit) microbial invasion following tail or skin loss? Early evidence points towards the production of anti-microbial peptides (such as beta-defensins) as an important adaptation with obvious biomedical implications (Alibardi et al., 2012). Although genomic and transcriptomic data are now available for several tail-regenerating species, it would be instructive to compare these findings with those of closely related but regeneration-incompetent lizards. This would help unravel which molecular players are part of the regenerative program, and which are involved in the non-regenerative healing milieu. Furthermore, these data would also provide important targets for gene-editing strategies (such as CRISPR), with the long-term goal of promoting, if not creating, regenerative competence.

Acknowledgements

We gratefully acknowledge members of the Vickaryous lab, past and present, as well as Dr Charlotte Rutledge and two anonymous reviewers for insightful comments, and Henrik Bringsøe (www.natureswindow.dk) for permission to use his image of the Dwarf bronze gecko (*Ailuronyx tachyscopaeus*) in Fig. 1.

Competing interests

The authors declare no competing or financial interests.

Funding

Financial support was provided by a Natural Sciences and Engineering Research Council of Canada Discovery Grant (400358 to M.K.V.).

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